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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,770	12/17/2001	Yoshihito Ikeda	F-7178	2012

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EXAMINER	
PRATS, FRANCISCO CHANDLER	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 08/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/018,770	**Applicant(s)** IKEDA ET AL.	
	Examiner Francisco C. Prats	**Art Unit** 1651	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 July 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *01 August 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,4,6-8,10-14 and 19*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 7-27-05
13. ☒ Other: PTO-892 attached.

ATTACHMENT TO ADVISORY ACTION

The response filed July 27, 2005, has been received and entered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

All of applicant's argument has been fully considered but is not persuasive of error. Applicant urges that the claims under examination are directed to "a composition that overcomes problems associated with degradation of the phosphatidyl choline (PC) moieties surrounding the SOD." Response of July 27, 2005, page 2. Thus, applicant urges in effect that the reason they are combining sucrose with PC-SOD is different than the reason sucrose was combined with SOD in the past.

However, note specifically that claimed subject matter must be held obvious if the prior art suggests its practice, even if the prior art's rationale for practicing the claimed subject matter is different than applicant's. See MPEP § 2144, subsection entitled "RATIONALE DIFFERENT FROM APPLICANT'S IS PERMISSIBLE", and cases cited therein. As noted in previous office actions, and herein below, and well established on the record, the use of sucrose as a protein stabilizing agent for PC-SOD is considered obvious, in view of the art-recognized stabilizing effect of sucrose on proteins, including SOD, in storage processes using lyophilization (i.e. freeze-drying).

The fact that the art-suggested rationale for making the claimed combination of two ingredients is different than applicant's does not make the claimed composition any less obvious, absent evidence of some unexpected result coming from the claimed combination.

Applicant's argument also does not reflect the true scope of the subject matter actually recited in the claims. Contrary to applicant's argument, the claims do not recite that the SOD molecule is surrounded by PC. Rather, formula (I) in claim 1 specifically recites that the number of lecithin derivatives may be as low as "1 or more." An SOD molecule having 1, or even 2, phosphatidylcholine (PC) moieties attached to it, would not be surrounded by PC. This is particularly true in view of the fact that depending on the source, human superoxide dismutase can have a molecular weight ranging anywhere from about 32,500 daltons to 40,000 daltons (undenatured form, see JP '882 Translation, page 8, line 9), whereas the molecular weight of phosphatidylcholine is about 800 daltons, or even less, depending on the fatty acids present in the molecule. A single 800 dalton phosphatidylcholine molecule cannot surround a 32,500 to 40,000 dalton superoxide dismutase molecule.

Applicant also argues that JP '882 teaches that dimerization of SOD is a problem that must be avoided to prevent

allergenic effects, and that there is "no problem with denaturation of SOD during freezing and thawing or freeze-drying, unless a denaturant is added," and that sucrose, among other compounds, may be used to prevent dimerization of SOD without also causing denaturation. Response of July 27, 2005, page 2.

Contrary to applicant's argument, JP '882 clearly discloses that "[d]enaturation of bovine SOD is 25 percent or greater with freeze-drying." JP '882 Translation, page 4, first full paragraph. Moreover, as noted in the previous office action, JP '882 also clearly states that "even with the combination of aldose monosaccharides such as galactose, arabinose, glucose, and the like to human SOD prior to freeze-drying, ***analysis by anion-exchange chromatography reveals denaturation*** (Comparative Example 3)." JP '882 Translation, page 4, second full paragraph, emphasis added. Thus, contrary to applicant's argument with respect to the assertion that there is no denaturation of SOD during freezing and thawing, JP '882 discloses denaturation to be a problem when storing SOD, both bovine and human.

Applicant's new argument (Response of July 27, paragraph spanning pages 2 and 3), that JP '882 teaches that there is no denaturation problem with SOD unless a denaturant is added, and

that the aldose monosaccharide moieties used previously in preserving SOD are denaturants, is noted. However, as noted above, JP '882 discloses that bovine SOD clearly suffers from significant, i.e. "25 percent or greater" denaturation, when freeze-dried. There is no mention of any denaturant which causes this effect in bovine SOD. In view of the fact that all of applicant's claims, except claim 7, encompass the use of bovine SOD, applicant's argument regarding the disclosure of JP '882 is clearly erroneous with respect to all claims except for claim 7.

With respect to human SOD, note again that only claim 7 is directed to the use of human SOD. Thus, with respect to all claims except claim 7, applicant's argument regarding the denaturation of human SOD, and whether it is caused by aldose monosaccharides, is not relevant. With respect to claim 7 and human SOD, JP '882 does not state, as asserted by applicant, that the monosaccharide moieties thought to be useful as preservative agents are denaturants. Nowhere does the JP '882 translation contain the word "denaturant." Rather, JP '882 addresses the issue directly, stating that "the use of aldose monosaccharides to prevent denaturation of human SOD during freezing or freeze-drying is undesirable." JP '882 Translation, page 4, second full paragraph. Saying that certain compounds

are not desirable enzyme preservative agents is not the same as saying that those agents cause denaturation.

Applicant's assertion, that JP '882 teaches that aldose monosaccharides act as denaturants to human SOD, is based on the fact that, in the absence of aldose monosaccharides, DEAE analysis of freeze-dried and thawed human SOD "did not reveal any denaturation of human SOD (Fig. 12)" (JP '882 Translation, Comparative Example 2), whereas, according to applicant, Comparative Examples 3-5, all of which use aldose monosaccharides as preservative agents, demonstrate that the aldose monosaccharides "all caused denaturation." Response of July 27, 2005, page 3. Presumably applicant's argument is based on Table 2 on page 17 of the JP '882 Translation, wherein Comparative Example 2 is listed as having "None" in the "Denaturation" column, whereas Comparative Examples 3-5 are listed as having "Present" in the "Denaturation" column.

However, applicant's argument entirely ignores the fact that each of Comparative Examples 3-5 explicitly states that "DEAE analysis ***did not reveal any denaturation*** of human SOD." (Emphasis added.) *See,* JP '882 Translation at page 16, lines 4 and 5, Comparative Example 3 ("DEAE analysis ***did not reveal any denaturation*** of human SOD (Fig. 9)")(emphasis added); *see also, id.,* at page 16, lines 14 and 15, Comparative Example 4 ("DEAE

analysis ***did not reveal any denaturation*** of human SOD (Fig. 10")(emphasis added)); *see also, id.,* at page 16, line 25 through page 17, line 1, Comparative Example 5 ("DEAE analysis ***did not reveal any denaturation*** of human SOD (Fig. 11")(emphasis added). Thus, contrary to applicant's argument, and even conceding the ambiguity between the data presented in Table 2 and the written description of the results of the Comparative Examples, there is no clear evidence presented in JP '882 that aldose monosaccharides actually cause denaturation of human SOD. Again, a disclosure that aldose monosaccharides are not desirable preservatives for SOD does not mean that aldose monosaccharides cause denaturation of human SOD.

Applicant argues yet again that there is nothing on the record to suggest that PC-SOD dimerizes or forms allergenic materials during freeze-drying and/or freezing/thawing operations, and that there is evidence on the record that SOD and PC-SOD are substantially different materials that behave substantially differently. Response of July 27, 2005, pages 3 and 4. However, contrary to applicant's argument, it is a fact that the protein portions of PC-SOD and SOD are identical. Moreover, PC-SOD and SOD have identical catalytic properties. As pointed out above SOD is a 32,500 to 40,000 dalton protein. The PC-SOD, as recited in applicant's claims, contains a single

pendant phosphatidylcholine group of about 800 daltons attached to the much larger protein molecule. The pendant PC group is therefore much smaller than the protein to which it is attached. Thus, based on the fact that the protein portion of the two molecules is identical, and that the single attached PC molecule is a small portion of the total PC-SOD, one of ordinary skill in the art would have expected the physical properties of PC-SOD to have been fairly similar to the physical properties the underivatized SOD.

It is conceded that one of ordinary skill would have recognized that attaching PC to SOD modifies the ***biological properties*** of the compound by increasing its therapeutic availability. However, based on the expected commonality of ***physical properties*** between PC-SOD and SOD, reflected as a function of the common structural compositions discussed above, one of ordinary skill seeking to prepare a lyophilized (freeze-dried) form of PC-SOD as suggested by JP '279 (paragraph [0028]) clearly would not have ignored prior art disclosing ingredients suitable for use in lyophilized forms of the closely related compound SOD. Rather, the first prior art the artisan of ordinary skill would have consulted when seeking to prepare lyophilized formulations of PC-SOD would in fact have been prior art directed to preparing lyophilized forms of SOD.

Applicant further argues that PC-SOD is derived from SOD by reacting functional groups on the SOD with phosphatidylcholine, "thereby eliminating reactive sites responsible for dimerization of unmodified SOD." Response of July 27, 2005, page 3. Applicant argues still further that "it is well recognized by those having ordinary skill in the art that such modifications also create steric and conformational effects that would cause PC-SOD to behave differently from SOD." *Id.* However, applicant fails to provide any evidentiary support for the asserted elimination of dimerization sites and well known steric hindrance. In this regard note specifically that argument by counsel is not a sufficient substitute for actual evidence. See, e.g., MPEP § 2145, subsection "I", and cases cited therein. Moreover, applicant's argument is undermined by the breadth of the claims under examination, which, as discussed above, encompass the presence of ***one*** relatively small PC moiety on the much larger SOD molecule. In view of the actual structures of the entities involved, it is clear that evidentiary support of the presently unsupported assertions is appropriate.

Further still, the fact that U.S. Pat. 5,762,929, states that PC-SOD does not have "antigenicity" when administered ('929 patent, column 1, lines 60-61), simply does not mean that PC-SOD does not suffer from dimerization when subjected to

lyophilization. There is no disclosure that the PC-SOD described in the "antigenicity" statement in U.S. '929 was lyophilized. It is simply not clear that the "antigenicity" statement in U.S. '929 is relevant to the lyophilization of PC-SOD, and whether one would have used the sucrose preservative for SOD when lyophilizing PC-SOD.

In sum, applicant is incorrect in stating that denaturation is not an issue when freeze-drying SOD. As discussed above, JP '882 clearly discloses that "[d]enaturation of bovine SOD is 25 percent or greater with freeze-drying." JP '882 Translation, page 4, first full paragraph. Whether this denaturation is caused by proteases as posited in the quoted statement (3) on page 4 of the Response of July 27, 2005, or other causes, the fact remains that the enzyme is denatured when frozen and thawed. JP '882 clearly states that sucrose prevents this denaturation. Moreover, as discussed above, JP '882 may be ambiguous as to whether denaturation occurs when *human* SOD is freeze-dried and thawed, because the description of Comparative Examples 3-5 state that no denaturation took place, whereas Table 2 suggests that denaturation was "present." Either way, however, contrary to applicant's argument, there is nothing suggesting that aldose monosaccharides act as active denaturants of human SOD.

Lastly, only claim 7 recites human PC-SOD. Thus, the issue of whether one of ordinary skill would have expected the advantages of sucrose as a stabilizer in freeze-dried human SOD compositions, disclosed by JP '882, to have been applicable to the freeze-dried PC-SOD compositions of JP '279, pertains only to claim 7. As discussed above, given the common structures and properties of SOD and PC-SOD, one of ordinary skill seeking to prepare a freeze-dried form of PC-SOD as suggested by JP '279 (paragraph [0028]) clearly would not have ignored prior art disclosing ingredients suitable for use in lyophilized forms of the closely related compound SOD. Rather, the first prior art the artisan of ordinary skill would have consulted when seeking to prepare lyophilized formulations of PC-SOD would in fact have been prior art directed to preparing lyophilized forms of SOD.

No claims are allowed. U.S. Pat. Nos. 4,966,774 and 3,637,640 are cited to further show the state of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C. Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Francisco C. Prats
Primary Examiner
Art Unit 1651

FCP